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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,016	05/07/2001	Helge Voelkel	24498	3060

20529 7590 01/14/2004

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EXAMINER

SWOPE, SHERIDAN

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/744,016

Applicant(s)

VOELKEL, HELGE

Examiner

Sheridan L. Swope

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 5-23 is/are pending in the application.
- 4a) Of the above claim(s) 23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 5-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Applicant's Request for Continuing Examination, received December 1, 2003, is acknowledged. It is acknowledged that applicants have amended Claim 18 and cancelled Claim 4. Claim 23 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Applicants state on page 3, line 2-3, of their Request for Continuing Examination that Claims 1, 2, and 14 have been amended; however, the instant claims are identical to those in the prior amendment received September 29, 2003. Therefore Claims 1, 2, and 14 are not considered to be amended by Applicants Request for Continuing Examination, received December 1, 2003. Claims 1-3 and 5-22 are hereby reconsidered.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of Claims 1-3 and 5-22 under 35 U.S.C. 112, first paragraph for lack of enablement is maintained. As stated in the First Action on the Merits for the original filing of this application, the specification is enabling for methods of screening for modulators of calcineurin activity in the presence of SOD as well as binding of calcineurin and SOD using the calcineurin and SOD variants of Examples 20-25. However, the specification is not enabling for methods of using any form of calcineurin or any form of SOD.

Applicants traverse the rejection under 35 U.S.C. §112, first paragraph with the following arguments, which are found not to be persuasive.

(1) The discussion of "variants" and "a large genera proteins" is only appropriate to an application which claims methods for using any form of calcineurin and/or any form of SOD. However, these arguments reflect fundamental misunderstanding of the inventive subject matter, because the inventive subject matter is concerned with a method for screening for activity of only one Calcineurin/SOD combination at a time. A discussion about variants is irrelevant to the claimed invention.

Reply: It is acknowledged that the claims recite methods for screening for activity of only one Calcineurin/SOD combination at a time. However, the claims recite methods for screening for activity of any Calcineurin and any SOD in combination. Thus, the claims recite methods using any Calcineurin, any SOD, any variants thereof, and any combination thereof. Said Calcineurin and SOD as well as said variants represent large genera of proteins. Furthermore, methods using any combination thereof, represents a large genus of combinations.

(2) The minimal experimentation required to determine whether a particular Calcineurin/SOD combination has the desired activity is nothing more than routine experimental control which may, optionally, be completed before proceeding with the claimed methods for screening for modulators of that activity. Any chosen combination of calcineurin and SOD will either have an activity of interest or not. The experimentation required to run a positive control to determine whether there is such activity is not "undue experimentation."

Reply: It is acknowledged that assays for testing of binding between calcineurin and SOD as well as analysis of calcineurin enzymatic activity are routine in the art. However, screening the large genus of calcineurin, the large genus of SOD, and the large genus of calcineurin/SOD combinations, as recited by the instant claims, is not routine in the art. If a

large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated, the specification does not establish: (A) regions of the protein structure which may be modified without effecting the desired activity of calcineurin or SOD; (B) the general tolerance of the desired activity of calcineurin and SOD to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any calcineurin or SOD residues with an expectation of obtaining the desired activity; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices of calcineurin, SOD, and combinations thereof are likely to be successful.

(3) The claimed inventive subject matter assumes that one will screen for modulators of the desired activity on in those Calcineurin/SOD combinations which have an activity one wishes modulate.

Reply: It is acknowledged that one will screen for modulators of the desired activity on those Calcineurin/SOD combinations, which have an activity one wishes modulate. However, as described for point (2), the specification does not provide sufficient guidance to enable one of skill in the art to know which of the essentially unlimited number of Calcineurin/SOD combinations can be successfully used in the recited methods.

(4) Further, however routine determination of activity of particular Calcineurin/SOD combination may be, this step is not required by claimed subject matter, and one may screen for modulators of inactive Calcineurin/SOD combinations as well.

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Reply: It is acknowledged that one could use catalytically inactive calcineurin in methods directed to testing modulators of Calcineurin/SOD binding. However, to test for modulators of Calcineurin/SOD binding, as recited in Claims 1-3 and 5-22, the Calcineurin/SOD combination used must have binding activity. Furthermore, to test for modulators of calcineurin enzymatic activity for any Calcineurin/SOD combination, as recited in Claims 14-22, the calcineurin must have enzymatic activity.

Therefore, Rejection of Claims 1-3 and 5-22 under 35 U.S.C. 112, first paragraph for lack of enablement is maintained.

Rejection of Claims 1-3 and 5-22 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is also maintained. The specification fails to describe the structure of sufficient representative species of the large genera of all proteins having the desired calcineurin or SOD activity, and combinations thereof, such that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejection of Claims 1-5, 9, 13-16, 18, 19, and 21, under 35 U.S.C. 102(b) as being anticipated by Wang et al, 1996 is maintained. The reasons for this rejection are described in the First Action on the Merits, mailed November 19, 2002, and the Final Rejection mailed July 1, 2003.

In support of their request for withdrawal of said rejection, Applicants provide the following arguments, which are not found to be persuasive.

(1) The '989 patent fails teach the claimed subject matter. Applicant's claims as presently amended are directed to a method for screening for a modulator of calcineurin enzymatic activity, characterized in that a direct interaction between calcineurin and superoxide dismutase is monitored. By contrast, Wang, et al. disclose only that calcineurin and SOD co-elute, in part, on gel filtration. The word "complex" or the concept of a direct relationship is not disclosed in Wang, et al. to describe the calcineurin/SOD relationship.

To constitute anticipation under U.S.C. 102, material elements of a claim must be formed [found] in one prior art source. In re Marshall, 577 F.2d 301, 198 USPQ 344 (CCPA 1978): In re Kalm, 378 F. 2d 959, 154 USPQ 10 (CCPA 1967). As the Examiner admits, Wang, et does not disclose the direct complex formation and activity as claimed herein. Thus,...wang et does not anticipate the present claims.

Reply: It is unclear what Applicants mean by "the '989 patent", as no patent was cited in the rejection. Rejection of Claims 1-5, 9, 13-16, 18, 19, and 21, under 35 U.S.C. 102(b) is based on Wang et al, 1996 Nature. 1996 Oct 3;383(6599):434-7. Claims 1-5, 9, 13- 16, 18, 19, and 21, as written, do not limit the scope of the invention to methods for screening of modulators of calcineurin enzymatic activity wherein said methods are characterized in that a direct interaction between calcineurin and SOD is monitored. To do so would require purification of calcineurin and SOD before formation of the Calcineurin/SOD complex, as recited in Claims 10-12. In fact, Claim 1 seems to teach away from methods of detecting modulators of a direct interaction by reciting "-formation of a complex comprising at least calcineurin and superoxide dismutase..."

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on line 6. As taught by Wang et al, when calcineurin (CNs) is isolated by chromatography over Sephadex G-50 (Fig 1; CNs) and the isolated CNs rechromatographed over Sephadex G-100, SOD elutes in fractions 35-60 from the Sephadex G-100 column. Based on said teachings, a person of ordinary skill in the art would assume that SOD was complexed with calcineurin during chromatography over the G-50 column.

Therefore, rejection of Claims 1-5, 9, 13-16, 18, 19, and 21, under 35 U.S.C. 102(b) as being anticipated by Wang et al, 1996 is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-5 13-16, 18, 19, and 21, are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al, 1996 in view of Boopathy et al, 1986. The teachings of Wang et al are described above and in the prior actions. Wang et al do not teach testing the effect of a modulator on the direct interaction of calcineurin with SOD. However, testing the effect of modulators on the direct interaction between an enzyme and an activator is common in the art. For example, Boopathy et al teach that haemin binds to and activates purified cyclooxygenase (Figs 3 and 2, respectively), while aspirin blocks said binding (Fig 4 and pg 377, lines 8-16). Wang et al teaches that calcineurin and SOD form a complex and that, activation of calcineurin by SOD can be blocked by an inhibitor (Fig 5). It would be obvious to a person of ordinary skill in the art to test whether any inhibitor blocks direct binding and activation of calcineurin by

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SOD. Motivation to do is provided by the advantage of knowing whether the inhibitor affects calcineurin by interrupting a direct interaction between the enzyme and SOD. The results of such a test would be useful in designing inhibitors of calcineurin. The expectation of success is high as purification of enzymes and testing the effects of potential modulators on purified enzymes is known in the art. Therefore, Claims 1-5 13-16, 18, 19, and 21, are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al, 1996 in view of Boopathy et al, 1986.

Rejection of Claims 6-8 and 17 under 35 U.S.C. 103(a) as being unpatentable over Wang et al, 1996 in view of Brown et al, 1997, rejection of Claim 9 under 35 U.S.C. 103(a) as being unpatentable over Wang et al, 1996 in view of Woodrow et al, 1993, rejection of Claims 10-12 over Wang et al, 1996 in view of Lau et al, 1996 or Robbins et al, 1993 and further in view of Aramburu et al, 1998, and rejection of Claims 5, 15, and 17 under 35 U.S.C. 103(a) as being unpatentable over Wang et al, 1996 in view of admission of availability (Specification page 28 lines 21-24) are maintained. The reasons for these rejections are described in the prior action.

In support of Applicant's request that said rejections be withdrawn, they provide the following arguments, which are not found to be persuasive.

(1) As noted earlier, the Examiner concludes, without reference to a page and line number, that Wang, et al. "shows that calcineurin forms complex with SOD." Contrary to the Office Action, Wang, et al. shows only that calcineurin co-elutes with SOD.

Reply: As described above for the rejection of Claims 1-5, 9, 13-16, 18, 19, and 21, under 35 U.S.C. 102(b) as being anticipated by Wang et al, 1996, based on the teachings of Wang et al (Figs 1 and 2), one of skill in the art would conclude that calcineurin and SOD form a complex.

(2) As presently amended, the inventive method is directed only to the monitoring of complex formation and not enzymatic activity.

Reply: Claims 14-22 are directed to measuring the enzymatic activity of calcineurin.

Therefore, rejection of Claims 6-8 and 17 under 35 U.S.C. 103(a) as being unpatentable over Wang et al, 1996 in view of one of Brown et al, 1997, rejection of Claim 9 under 35 U.S.C. 103(a) as being unpatentable over Wang et al, 1996 in view of Woodrow et al, 1993, rejection of Claims 10-12 over Wang et al, 1996 in view of Lau et al, 1996 or Robbins et al, 1993 and further in view of Aramburu et al, 1998, and rejection of Claims 5, 15, and 17 under 35 U.S.C. 103(a) as being unpatentable over Wang et al, 1996 in view of admission of availability (Specification page 28 lines 21-24) are maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696 (571-272-0943 after January 12, 2004). The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.

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